TRANSPERFECT | TRANSLATIONS
THE LEADER IN INTERNATIONAL COMMUNICATIONS

AFFIDAVIT OF ACCURACY

This is to certify the document, **Administrative data for Belmazol, 20 mg capsules, Addendum II, undated,** has been translated from Spanish into English by staff members of TransPerfect Translations familiar with both the Spanish into English languages and is to the best of our knowledge, ability and belief, a true and accurate translation.

Susan Christian
TransPerfect Translations, Inc.
15 Broad St., Suite 305
Boston, MA 02109

Sworn to before me this
22nd day of October 2004

Signature, Notary Public
Commonwealth of Massachusetts
Commission Expires August 14, 2009

[logo]

ADDENDUM II
Administrative Data

Name of the pharmaceutical specialty
BELMAZOL, 20 mg capsules

Registration number of the specialty
59829

Name of medicinal substance(s)/active principle(s)

OMEPRAZOLE

Pharmacotherapeutic Classification
A02BC01 - Omeprazole

Pharmaceutic form and dose
Hard capsule, 20 mg

Route of Administration

ORAL ROUTE

Containers/closures/administration devices

Bottle

Content of the containers (format) and national code

Format:	National Code:
BELMAZOL 20MG CAPSULES, 14 CAPSULES-NORMAL CONTAINER	884338
BELMAZOL 20MG CAPSULES, 28 CAPSULES-NORMAL CONTAINER	884320
BELMAZOL 20MG CAPSULES, 56 CAPSULES-NORMAL CONTAINER	830174

Shelf life:

Proposed Shelf Life	Shelf Life After Opening	Recommended Shelf Life
2 years		
2 years		
2 years		

Conditions for storage and preservation: —

Preserv. Cond.	Preserv. Cond. After Opening	TR Preserv. Cond.
ROOM TEMP.		
ROOM TEMP.		
ROOM TEMP.		

Dispensation requisites:
WITH REGULAR PRESCRIPTION.

Ministry of Health and Consumption
Spanish Drug and Health Products Agency

[logo]

Other Information: Pharmaceutical Specialty Ethics

Owner

Name:	LABORATORIOS BELMAC, S.A.
Address:	Teide, 4-ground floor. Polígono Empresarial La Marina (San Sebastian de los Reyes) – 28700 – Spain
Telephone:	91 659 32 80 Fax: 91 652 01 44

Entity which will market the specialty:

Name:	LABORATORIOS BELMAC, S.A.
Address:	Teide, 4-ground floor. Polígono Empresarial La Marina (San Sebastian de los Reyes) – 28700 – Spain
Telephone:	91 659 32 80 Fax: 91 652 01 44

Manufacturer(s) of the finished pharmaceutical specialty and place(s) of manufacture, including a description of the processes conducted

Name:	LABORATORIOS BELMAC, S.A.
Address:	Polígono Malpica c/C No. 4 (Zaragoza) – 50016 – Spain
Telephone:	976571784 Fax: 976572663
Task:	MANUFACTURE AND CONTROL

Site where batch release takes place

Name:	LABORATORIOS BELMAC, S.A.
Address:	Polígono Malpica c/C No. 4 (Zaragoza) – 50016 – Spain
Telephone:	976571784 Fax: 976572663

Manufacturer(s) of the medicinal substance(s)

Name: UQUIFA, S.A. (UNION QUIMICO FARMACEUTICA)
Address: Mallorca, 262 (Barcelona) – 08008 – Spain
Telephone: 934879477 Fax: 934880491
Registration of Active Principles (DMF): OW/103/96
Date of Update:
Date Sent:

Complete Qualitative and Quantitative Composition expressed by pharmaceutical form, administration unit or reference quantity.

Name of medicinal substance:	Quantity	Unit	General Characteristics

Ministry of Health and Consumption
Spanish Drug and Health Products Agency

[logo]

OMEPRAZOLE	20	MG	
Name of excipient:	**Quantity**	**Unit**	**General Characteristics**
SUGAR PELLETS (SACCHAROSE AND STARCH)	96.00	MG	
SODIUM CARBOXYMETHYL STARCH	4.20	MG	
SODIUM LAURYLSULFATE	5.98	MG	
CROSPOVIDONE	9.50	MG	
HYDROXYPROPYL METHYLCELLULOSE (HYPROMELLOSE)	6.00	MG	
COPOLYMER METHACRYLIC ACID AND ETHYL ACRYLATE (1:1)	40.91	MG	
ORANGE TABLET COATING (TRIETHYLCITRATE)	4.69	MG	
TALC	0.19	MG	
POTASSIUM OLEATE	1.49	MG	
TITANIUM DIOXIDE (CI=77891, E-171)	1.50	MG	

ANEXO II
Datos Administrativos.

Nombre de la especialidad farmacéutica
BELMAZOL, 20 mg cápsulas

Número de Registro de la especialidad
59629

Nombre de la(s) sustancia(s) medicinal(es)/principio(s) activo(s)

OMEPRAZOL

Clasificación Farmacoterapéutica
A02BC01 - Omeprazol

Forma farmacéutica y dosificación
Cápsula dura, 20 mg

Vía de Administración

VIA ORAL

Envases/cierres/dispositivos de administración

Frasco

Contenido de los envases (formato) y código nacional.

Formato:	Código Nacional:
BELMAZOL 20MG CAPSULAS, 14 CAPSULAS-ENVASE NORMAL	884338
BELMAZOL 20MG CAPSULAS, 28 CAPSULAS-ENVASE NORMAL	884320
BELMAZOL 20MG CAPSULAS, 56 CAPSULAS-ENVASE NORMAL	830174

Período de validez:

Val. Prep.	Val. Abrir	Val. Rec.
2 años		
2 años		
2 años		

Condiciones de almacenamiento y conservación:

Cond.Conserv.	C.Conserv. Abr.	C.Conserv. TR
AMBIENTE		
AMBIENTE		
AMBIENTE		

Requisitos de dispensación:
CON RECETA ORDINARIA

MINISTERIO DE SANIDAD Y CONSUMO
Agencia española de medicamentos y productos sanitarios

Otra información: Especialidad Farmacéutica Ética

Titular

Nombre:: LABORATORIOS BELMAC, S.A.
Dirección: Telde, 4-planta baja. Polígono Empresarial La Marina (San Sebastian de los Reyes) - 28700 - España
Teléfono: 91 659 32 80 Telefax: 91 652 01 44

Entidad que va a comercializar la especialidad:

Nombre:: LABORATORIOS BELMAC, S.A.
Dirección: Telde, 4-planta baja. Polígono Empresarial La Marina (San Sebastian de los Reyes) - 28700 - España
Teléfono: 91 659 32 80 Telefax: 91 652 01 44

Fabricante/s de la especialidad farmacéutica terminada y lugar/es de fabricación, incluyendo una descripción de los procesos que realizan

Nombre: LABORATORIOS BELMAC, S.A.
Dirección: Polígono Malpica c/C nº 4 (Zaragoza) - 50016 - España
Teléfono: 976571764 Telefax: 976572663
Tarea: FABRICACIÓN Y CONTROL

Lugar donde se libera el lote - Site where batch release takes place

Nombre: LABORATORIOS BELMAC, S.A.
Dirección: Polígono Malpica c/C nº 4 (Zaragoza) - 50016 - España
Teléfono: 976571764 Telefax: 976572663

Fabricante/s de la/s sustancia/s medicinal/es

Nombre: UQUIFA, S.A. (UNION QUIMICO FARMACEUTICA)
Dirección: Mallorca, 262 (Barcelona) - 08008 - España
Teléfono: 934879477 Telefax: 934880491
Registro Ppios. Activos (DMF): OW/103/96
Fecha Actualización:
Fecha Envío:

Composición Cualitativa y Cuantitativa completa expresada por forma farmacéutica, unidad de administración o cantidad de referencia.

Nombre de sustancia medicinal:	Cantidad	Unidad	Caract. Grles

MINISTERIO DE SANIDAD Y CONSUMO
Agencia española de medicamentos y productos sanitarios

OMEPRAZOL	20	MG	
Nombre de excipiente:	Cantidad	Unidad	Caract.Grlas
ESFERAS DE AZUCAR (SACAROSA Y ALMIDON)	96,00	MG	
CARBOXIMETILALMIDON SODICO	4,20	MG	
LAURILSULFATO SODICO	5,88	MG	
CROSPOVIDONA	9,60	MG	
HIDROXIPROPIL METILCELULOSA (HIPROMELOSA)	8,00	MG	
COPOLIMERO AC METACRILICO Y ACRILATO ETILO (1:1)	40,91	MG	
NARANJA COBERTURA COMPR. (TRIETILCITRATO	4,69	MG	
TALCO	0,19	MG	
OLEATO POTASICO	7,49	MG	
DIOXIDO DE TITANIO (CI=77891, E-171)	1,80	MG	

MINISTERIO DE SANIDAD Y CONSUMO
Agencia española de medicamentos y productos sanitarios

TRANSPERFECT | TRANSLATIONS
THE LEADER IN INTERNATIONAL COMMUNICATIONS

AFFIDAVIT OF ACCURACY

This is to certify the document, **Preparation and sale of pharmaceutical specialty, Belmazol, Registration No. 59.829- Undated,** has been translated from Spanish into English by staff members of TransPerfect Translations familiar with both the Spanish into English languages and is to the best of our knowledge, ability and belief, a true and accurate translation.

Susan Christian
TransPerfect Translations, Inc.
15 Broad St., Suite 305
Boston, MA 02109

Sworn to before me this
22nd day of October 2004

Signature, Notary Public
Commonwealth of Massachusetts
Commission Expires August 14, 2009

MINISTRY OF HEALTH AND CONSUMPTION **R.D. 424/[illegible]**

GENERAL DEPARTMENT OF PHARMACY AND HEALTH PRODUCTS

By the powers vested in me and pursuant to current legislation, I AUTHORIZE for preparation and sale the pharmaceutical specialty, in the terms detailed below:

Name of the pharmaceutical Specialty	Registration No.
BELMAZOL, capsules	59.829

Pharmaceutical form	Therapeutic group	Shelf life
Capsules	A02B2	3 years

Preservation requisites
NORMAL

Formats	Prices	National code No.
14 capsules	Wholesale = 2,500 Retail = 4,053 Retail Price VAT = 4,174	748632
	Wholesale = Retail = Retail Price VAT =	
	Wholesale = Retail = Retail Price VAT =	

Conditions for authorization and requisites for dispensation
WITH MEDICAL PRESCRIPTION

1. Owner Laboratory or Importer Laboratory	Registration No. with DGFM
BELMAC, S.A.	3.150
Address P° de la Castellana, 149. 28046 Madrid	

2. Manufacturing Laboratory (If different from 1)

Marketing Laboratory (If different from 1)

Complete quantitative composition (CID for the components which have obtained it):
Per capsule

ACTIVE PRINCIPLE

Omeprazole	20.00	mg

EXCIPIENTS

Neutral (saccharose and corn starch)	177.00	mg
Mannitol	16.70	mg
Sodium salt of carboxymethyl oxystarch (Explotab)	1.30	mg
Hydroxypropyl Methylcellulose phthalate (HP50) ..	6.60	mg
Sodium laurylsulfate	0.60	mg
Hydroxypropyl methylcellulose (Pharmacoat)	6.00	mg
Talc	0.20	mg
Methacrylic polymers (Eudragit L)	6.60	mg

Space reserved for a copy of the authorized package insert and technical sheet

[illegible stamp]

Belmazol **[illegible]**
OMEPRAZOLE **Capsules**

PROPERTIES:
Omeprazole activates [illegible] the hydrogen ion pump in the gastric parietal cell. Therefore, it reduces the secretion of gastric acid by a new mechanism of action. It rapidly activates and produces reversible control of the secretion of stomach acid with only one daily dose.

COMPOSITION PER CAPSULE:

Omeprazole	.....	20	mg
Excipients Saccharose	.....	108	mg
Other	.....		[illegible]

INDICATIONS:
- Short-term treatment of duodenal ulcer.
- Zollinger Ellison Syndrome.
- Gastric ulcer.
- Reflux esophagitis.

DOSAGE:
- Duodenal ulcer. The recommended dose is 20 mg (one capsule once daily). In most of these patients with duodenal ulcer, rapid relief of symptoms is obtained, and healing occurs in the first two weeks of treatment. In patients whose ulcers were not able to be totally healed by this initial cycle, they generally show healing during an additional two-week treatment period.
In patients with duodenal ulcer resistant to other treatment regimens, a dose of 40 mg (2 capsules) once daily is started and generally healing is obtained in a period of 4 weeks.
Because experience with extended treatments is limited, maintenance treatment is not recommended until more data become available.
- Zollinger Ellison Syndrome: The initial recommended dose is 60 mg (3 capsules) once daily. This must be individually adjusted, and the treatment must be continued while this is indicated clinically. More than 90% of patients with severe disease and with inadequate response to other treatments have been effectively controlled with doses of [illegible] to [illegible] mg daily.
If the dose exceeds 80 mg daily, it must be divided and administered in two doses per day, every 12 hours.
- Children: There is no pediatric experience because it is not recommended in children.
- Elderly: In elderly patients it is not necessary to adjust the dosage indicated above.
- Altered renal and/or hepatic function: In patients with deterioration of renal function or hepatic function, adjustments in dosing are not necessary.

MINISTERIO DE SANIDAD Y CONSUMO

R.D. 424/88

DIRECCION GENERAL DE FARMACIA Y PRODUCTOS SANITARIOS

Haciendo uso de las atribuciones que me están conferidas y en cumplimiento de lo dispuesto en la legislación vigente, AUTORIZO para su preparación y venta la especialidad farmacéutica, en los términos que se detallan a continuación:

Nombre de la Especialidad farmacéutica	Nº de Registro
BELMAZOL, cápsulas	59.829

Forma farmacéutica	Grupo terapéutico	Plazo de caducidad
Cápsulas	A02B2	3 años

Requisitos de conservación
NORMALES

Formatos	Precios	Nº de código nacional
14 cápsulas	PVL = 2.500 PVP = 4.053 PVP IVA = 4.174	748632
	PVL = PVP = PVP IVA =	
	PVL = PVP = PVP IVA =	

Condiciones de autorización y requisitos de dispensación
CON RECETA MEDICA

1. Laboratorio Titular o Laboratorio importador	Nº de registro en la DGFM
BELMAC, S.A.	3.150

Domicilio
Pª. de la Castellana, 149. 28046 Madrid

2. Laboratorio *Fabricante* (Si difiere de 1)

Laboratorio comercializador (Si difiere de 1)

Composición cuantitativa completa (DCI para los componentes que la tengan concedida):
Por cápsula

PRINCIPIO ACTIVO

Omeprazol	20,00 mg

EXCIPIENTES

Neutros (sacarosa y almidón de maíz)	177,00 mg
Manitol	16,70 mg
Sal sódica de coarboximetil oxialmidón (Explotab)	1,30 mg
Ftalato de hidroxipropilmetil celulosa (HP50) ..	6,60 mg
Laurilsulfato sódico	0,60 mg
Hidroxipropil metilcelulosa (Farmacoat)	6,00 mg
Talco	0,20 mg
Polímeros metacrílicos (Eudragit L)	6,60 mg

Espacio reservado para un ejemplar del prospecto y ficha técnica autorizados

Belmazol

OMEPRAZOL

Cápsulas

PROPIEDADES:
El omeprazol actua inhibiendo la bomba de hidrogeniones en la célula parietal gástrica. Así, reduce la secreción de ácido gástrico a través de un mecanismo de acción nuevo. Actua rapidamente y produce un control reversible de la secrecion de ácido del estomago con solo una dosis diaria.

COMPOSICION POR CAPSULA:

Omeprazol	.....	20 mg
Excipientes: Sacarosa	.....	108 mg
Otros	.....	c.s.

INDICACIONES:
— Tratamiento a corto plazo de la ulcera duodenal
— Sindrome de Zollinger Ellison.
— Ulcera gastrica.
— Esofagitis por reflujo.

POSOLOGIA:
— Ulcera duodenal. La dosis recomendada es de 20 mg (una cápsula) una vez al dia. En la mayoria de estos pacientes con ulcera duodenal, se consigue rapidamente un alivio de los sintomas, y la cicatrización ocurre en los dos primeras semanas de tratamiento. En los pacientes cuyas ulceras no hayan podido cicatrizar totalmente tras este ciclo inicial, generalmente presentan la cicatrizacion durante un periodo adicional de dos semanas de tratamiento.
En pacientes con ulcera duodenal, refractarios a otros regimenes de tratamiento, se usó una dosis de 40 mg (2 capsulas) una vez al dia, y generalmente se consiguió la cicatrizacion en el periodo de 4 semanas.
Debido a que la experiencia en los tratamientos prolongados es limitada, no se recomienda el tratamiento de mantenimiento hasta que no se posean mas datos.
— Sindrome de Zollinger Ellison: La dosis inicial recomendada es de 60 mg (3 capsulas) una vez al dia. Esta se debe ajustar individualmente y debe continuarse el tratamiento mientras que este indicado clinicamente. Más del 90 % de pacientes con enfermedad grave y con respuesta inadecuada a otros tratamientos, se han controlado eficazmente con dosis de 20 a 120 mg diarios.
Si la dosis sobrepasa a los 80 mg diarios, esta debe dividirse y administrarse en dos tomas al dia, una cada 12 horas.
— Niños: No hay experiencia en pediatria, por lo que no se recomienda en niños.
— Ancianos: En pacientes de edad no es necesario realizar ajustes en la dosificacion vista anteriormente.
— Funcion renal y/o hepática alteradas: En pacientes con deterioro de la función renal o la funcion hepática no son necesarios ajustes en la dosificación.

TRANSPERFECT | TRANSLATIONS
THE LEADER IN INTERNATIONAL COMMUNICATIONS

AFFIDAVIT OF ACCURACY

This is to certify the document, **Request for modification of Belmazol, April 10, 2003,** has been translated from Spanish into English by staff members of TransPerfect Translations familiar with both the Spanish into English languages and is to the best of our knowledge, ability and belief, a true and accurate translation.

Susan Christian
TransPerfect Translations, Inc.
15 Broad St., Suite 305
Boston, MA 02109

Sworn to before me this
22nd day of October 2004

Signature, Notary Public
Commonwealth of Massachusetts
Commission Expires August 14, 2009

Laboratorios Belmac, S.A.

[stamp]
Spanish Drug Agency
APRIL 10, 2003
FEES

MINISTRY OF HEALTH AND CONSUMPTION
SPANISH DRUG AGENCY
GENERAL SUBDEPARTMENT OF DRUGS FOR HUMAN USE
Calle Huertas, 75
28014 MADRID

RE: Request for modification of marketing authorization of the specialty BELMAZOL 20 mg, capsules, No. 59.829, consisting of a change of excipients which do not affect bioavailability (202).

Juan Carlos Asensio Asensio, in the capacity of Pharmaceutical Technical Director of Laboratorios BELMAC, S.A., recorded with the Spanish Drug Agency under number 3150, hereby

STATES:

1.- That Laboratorios BELMAC, S.A. is the owner of the specialty BELMAZOL 20 mg capsules registration No. 59.829, with the following composition per capsule:

Active principle:

Omeprazole (O.S.D.)	20.0 mg

Excipients:

Sugar pellets (saccharose and corn starch)	60.00 mg
Mannitol	70.00 mg
Sodium carboxymethyl starch	4.00 mg
Sodium laurylsulfate	3.04 mg
Povidone	8.00 mg
Hydroxypropyl Methylcellulose phthalate	59.20 mg
Myvacet (mixture of glycerin esters, acetic acid and fatty acids)	5.92 mg
Hydroxypropyl Methylcellulose	12.80 mg
Talc	0.24 mg

[letterhead]

Laboratorios Belmac, S.A.

2.- That this Laboratory wishes to request a change of excipients in the composition of said pharmaceutical specialty in order to eliminate the organic solvents used during the manufacturing process, without affecting the quality, safety and efficacy, proposing the following composition per capsule:

Active principle:

Omeprazole (O.S.D.)	20.0 mg

Excipients:

Sugar pellets (saccharose and corn starch)	96.00 mg
Sodium carboxymethyl starch	4.20 mg
Sodium laurylsulfate	5.98 mg
Povidone	9.50 mg
Potassium oleate	1.49 mg
Hydroxypropyl Methylcellulose	6.00 mg
Copolymer of methacrylic acid and ethyl acrylate 1:1	40.91 mg
Triethylcitrate	4.69 mg
Titanium dioxide	1.50 mg
Talc	0.19 mg

3.- That this Laboratory, in order to facilitate subsequent updates in the registration file as of the next month of July, presents complete and updated documentation in CTD format.

4.- That the proposed modification of excipients does not interfere with the current method of quantification of the content of Omeprazole and of the degradation products in the specialty, as established in the validation studies carried out.

5.- The specification of gastro-resistance (% not dissolved in pH 1.2±0.05, 2 hours) has been narrowed, proposing as limit, for release and shelf life, no less than 90%, in order to unify said criterion with the limit recommended in the USP Pharmacopoeia and with the indications of the Division of Chemistry and Pharmaceutical Technology of the General Subdepartment of Drugs for Human Use (Spanish Drug Agency).

[letterhead]

Laboratorios Belmac, S.A.

6.- That this Laboratory proposes a shelf-life period of 2 years, without need to specify special preservation conditions, based on:

- Stability data, conformant, of the composition proposed of 6 months under accelerated conditions (40±2°C and 75±5% RH) and data of 9 months under real time conditions (25±2°C and 60±5% RH).
- Available stability data under said conditions with the current formulation.

7.- That, as demonstrated in the documentation presented, the new composition proposed maintains and meets the criteria of an essentially similar product, pursuant to article 10.1(a)iii of European Directive 2001/83/EEC, as compared to the Spanish reference product Losec 20 mg capsules.

In light of the above,

REQUESTS:

The modification of the excipients of the specialty BELMAZOL 20 mg capsules, registration No. 59.829, with the following composition per capsule:

Active principle:

Omeprazole (O.S.D.)	20.0 mg

Excipients:

Sugar pellets (saccharose and corn starch)	96.00 mg
Sodium carboxymethyl starch	4.20 mg
Sodium laurylsulfate	5.98 mg
Povidone	9.50 mg
Potassium oleate	1.49 mg
Hydroxypropyl Methylcellulose	6.00 mg
Copolymer of methacrylic acid and ethyl acrylate 1:1	40.91 mg
Triethylcitrate	4.69 mg
Titanium dioxide	1.50 mg
Talc	0.19 mg

[letterhead]

Laboratorios Belmac, S.A.

For this reason, we enclose herewith:

- Receipt for payment of the fees corresponding to the modification of excipients.
- Addendum 2. Request for modification of a marketing authorization. Modification 202, change of excipients which do not affect bioavailability.
- Stability data of the current formulation.
- Forms 1, 2, 3 and 5, in CTD format.

This documentation is presented in duplicate, so that we are asking you to send a complete copy to the Division of Chemistry and Pharmaceutical Technology.

We are at your disposal for any clarification you may need, and I take this opportunity to send you my best regards.

Madrid, April 4, 2003.

[signature]

Juan Carlos Asensio Asensio
Pharmaceutical Technical Director

[letterhead]

Laboratorios Belmac, S.A.

agencia española del medicamento
10 ABR. 2003
TASAS

MINISTERIO DE SANIDAD Y CONSUMO
AGENCIA ESPAÑOLA DEL MEDICAMENTO
SUBDIRECCION GENERAL DE MEDICAMENTOS DE USO HUMANO
C/ Huertas, 75
28014 MADRID

ASUNTO: Solicitud de modificación de autorización de comercialización de la especialidad BELMAZOL 20 mg, cápsulas, Nº 59.829, consistente en un cambio de excipientes que no afectan la biodisponibilidad (202).

D. Juan Carlos Asensio Asensio en calidad de Director Técnico Farmacéutico de Laboratorios BELMAC, S.A., inscrito en la Agencia Española del Medicamento con el número 3150, por la presente,

EXPONE:

1.- Que Laboratorios BELMAC, S.A. es titular de la especialidad BELMAZOL 20 mg cápsulas nº registro 59.829, con la siguiente composición por cápsula:

Pricipio activo:

Omeprazol (D.O. E.)	20,0 mg

Excipientes:

Esferas de azucar (sacarosa y almidón de maiz)	60,00 mg
Manitol	70,00 mg
Carboximetilalmidón de sodio	4,00 mg
Laurilsulfato sódico	3,04 mg
Povidona	8,00 mg
Hidroxipropilmetilcelulosa ftalato	59,20 mg
Myvacet (mezcla de ésteres de glicerina ácido acético y ácidos grasos)	5,92 mg
Hidroxipropilmetilcelulosa	12,80 mg
Talco	0,24 mg

BELMAC
Teide, 4, planta baja • Parque Empresarial «La Marina» • 28700 SAN SEBASTIÁN DE LOS REYES (Madrid)
Tel.: 91 659 32 80* • Fax: 91 652 01 44 • www.belmac.com
Fábrica: Polígono Malpica, c/C, 4. 50016 ZARAGOZA • Tel.: 976 57 17 84 • Fax: 976 57 26 63

A-597A

Laboratorios Belmac, S.A.

2.- Que este Laboratorio desea solicitar un cambio de excipientes en la composición de dicha especialidad farmacéutica con objeto de eliminar los solventes orgánicos utilizados durante el proceso de fabricación, sin afectar la calidad, seguridad y eficacia, proponiendo la siguiente composición por cápsula:

Pricipio activo:

Omeprazol (D.O. E.)	20,0 mg

Excipientes:

Esferas de azúcar (sacarosa y almidón de maiz)	96,00 mg
Carboximetil almidón sódico	4,20 mg
Laurisulfato de sodio	5,98 mg
Povidona	9,50 mg
Oleato potásico	1,49 mg
Hidroxipropilmetilcelulosa	6,00 mg
Copolímero de ácido metacrílico y etil acrilato 1:1	40,91 mg
Trieltilcitrato	4,69 mg
Dióxido de titanio	1,50 mg
Talco	0,19 mg

3.- Que este Laboratorio, al objeto de facilitar posteriores actualizaciones en el dossier de registro a partir del próximo mes de Julio, presenta una documentación completa y actualizada en formato CTD.

4.- Que la modificación de los excipientes propuesta no interfiere en el modo actual de cuantificación del contenido de Omeprazol y de los productos de degradación en la especialidad, tal como queda constatado en los estudios de validación realizados.

5.- La especificación de gastro-resistencia (% no disuelto en pH 1,2±0,05, 2 horas) ha sido estrechada, proponiendo como límite, a la liberación y caducidad, no menos del 90%, con objeto de unificar dicho criterio con el límite recomendado en Farmacopea USP y con las indicaciones de la División de Química y Tecnología Farmacéutica de la Subdirección General de Medicamentos de Uso Humano (Agencia Española del Medicamento).

Teide, 4, planta baja • Parque Empresarial «La Marina» • 28700 SAN SEBASTIÁN DE LOS REYES (Madrid)

Laboratorios Belmac, S.A.

6.- Que este Laboratorio propone un periodo de caducidad de 2 años, sin necesidad de especificar condiciones especiales de conservación, en base a:
- Datos estabilidad, conformes, de la composición propuesta de 6 meses en condiciones aceleradas (40±2°C y 75±5% HR), y datos de 9 meses en condiciones a tiempo real (25±2°C y 60±5%HR).
- Datos disponibles de estabilidad en las mencionadas condiciones con la actual formulación.

7.- Que como queda demostrado en la documentación que se presenta, la nueva composición propuesta mantiene y satisface los criterios de producto esencialmente similar, de acuerdo al artículo 10.1(a)iii de la Directiva Europea 2001/83/EEC, frente al producto de referencia español Losec 20 mg cápsulas .

Por todo lo expuesto,

SOLICITA:

La modificación de excipientes en la especialidad BELMAZOL 20 mg cápsulas, nº registro 59.829, quedando definida su composición por cápsula:

Pricipio activo:	
Omeprazol (D.O. E.)	20,0 mg
Excipientes:	
Esferas de azúcar (sacarosa y almidón de maíz)	96,00 mg
Carboximetil almidón sódico	4,20 mg
Laurisulfato de sodio	5,98 mg
Povidona	9,50 mg
Oleato potásico	1,49 mg
Hidroxipropilmetilcelulosa	6,00 mg
Copolímero de ácido metacrílico y etil acrilato 1:1	40,91 mg
Trieltilcitrato	4,69 mg
Dióxido de titanio	1,50 mg
Talco	0,19 mg

Laboratorios Belmac, S.A.

Para lo cual, acompañamos a la presente:

- Impreso de pago de tasas correpondiente a la modificación de excipientes
- Anexo 2. Solicitud de modificación de una autorización de comercialización. Modificación 202, cambio de excipientes que no afectan la biodisponibilidad.
- Datos de estabilidad de la formulación actual.
- Módulos 1,2, 3 y 5, según formato CTD.

Esta documentación se presenta por duplicado, por los que rogamos remitan un copia completa a la División de Química y Tecnología Farmacéutica.

Quedando a su entera disposición para cualquier aclaración que precisen, aprovecho la ocasión para saludarles.

Madrid, 4 de Abril de 2003.

Juan Carlos Asensio Asensio
Director Técnico Farmacéutico

BELMAC
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TRANSPERFECT | TRANSLATIONS
THE LEADER IN INTERNATIONAL COMMUNICATIONS

AFFIDAVIT OF ACCURACY

This is to certify the document, **Manufacturing Contract Between Belmac and Ethypharm, March 23rd, 2000,** has been translated from Spanish into English by staff members of TransPerfect Translations familiar with both the Spanish into English languages and is to the best of our knowledge, ability and belief, a true and accurate translation.

Susan Christian
TransPerfect Translations, Inc.
15 Broad St., Suite 305
Boston, MA 02109

Sworn to before me this
22nd day of October 2004

Signature, Notary Public
Commonwealth of Massachusetts
Commission Expires August 14, 2009

MANUFACTURING CONTRACT

PRESENT

On the first part,

LABORATORIOS BELMAC, S.A. domiciled at Montearagón 9, 28033 Madrid, represented by its General Director Mr. Adolfo Herrera

Hereinafter **BELMAC**

And on the second part,

LABORATORIOS ETHYPHARM, S.A. domiciled at Marqués de Ensenada 16, 28004 Madrid, represented by its General Director Mr. Adolfo de Basilio

Hereinafter **ETHYPHARM**.

WHO STATE

1- That **BELMAC** is registered with the Spanish Office of Medications under number 3.150-E for the manufacture and commercialization of pharmaceutical products.

2- That **ETHYPHARM** is registered with the Spanish Office of Medications under number 3.328-E as possessor of authorizations for medications.

3- That both parties agree to enter into the present MANUFACTURING contract, in accordance with the terms of Royal Decree 1564/1992 of December 18, in respect of the product detailed in the Annexure, hereinafter the PRODUCT.

Both parties being interested in collaborating in this regard and in view of the current legislation pertaining to such cases, they do freely –

[signature]

AGREE

A- **BELMAC** undertakes to manufacture and deliver the PRODUCT manufactured in its installations, as detailed in the Annexure, upon prior purchase order of **ETHYPHARM.**

B- **BELMAC** will retain, or place these at **ETHYPHARM's** disposal, both the Production protocols and reference samples, together with all important information in order to evaluate the quality of the PRODUCT in the case of any claim [against it], or suspicion of any defect, or for any requirements of **ETHYPHARM.** Equally, both parties undertake to preserve the secrecy of all information they may exchange in respect of manufacture.

C- **BELMAC** will allow **ETHYPHARM** to access its installation as necessary for matters related to the present contract, in accordance with the Law and upon prior notification, with the date being subject to agreement by both parties.

D- **BELMAC** currently manufactures the product in accordance with good manufacturing practice, as per Law 15/1990 of December 20 (Law of Medications) and Royal Decree 1564/1992 of December 18.

E- The parties may assign their rights and obligations under the present contract to third parties, upon written consent of the other party, under such manner and conditions as determined by both parties. This contract shall not limit the manufacture of the product on the part of **BELMAC** for its own market and that of its clients.

F- Both parties expressly renounce any legal privileges they may have, and agree that the Courts of Madrid shall rule on any dispute which cannot be resolved in friendly fashion.

G- The present agreement shall remain in force for the period of two (2) years, being tacitly extendible for the same term except where one of the parties should claim otherwise in writing before expiry, with prior notice of four (4) months.

H- Manufacturing prices are to be agreed in a separate document, mutually agreed between both companies.

And in witness of which and to due legal effect, signatures are affixed to two copies of this document at Madrid, March 23, 2000.

For Laboratorios Ethypharm, S.A.
[signature]

For Laboratorios Belmac, S.A.
[signature]

ANNEXURE

OMEPRAZOLE microgranules as per patent No. 9207249

BELMAC may supply the PRODUCT to **ETHYPHARM** as a semi-manufactured product (microgranules), in bulk (capsules), a product in glass or aluminum, and as a finished product, on the proviso that the necessary Health Authorizations have previously been obtained.

AFFIDAVIT OF ACCURACY

This is to certify the document, **Letter of Purchase Undertaking, March 23, 2000,** has been translated from Spanish into English by staff members of TransPerfect Translations familiar with both the Spanish and English languages and is to the best of our knowledge, ability and belief, a true and accurate translation.

Susan Christian
TransPerfect Translations, Inc.
15 Broad St., Suite 305
Boston, MA 02109

Sworn to before me this
5th day of November 2004

Signature, Notary Public
Commonwealth of Massachusetts
Commission Expires August 14, 2009

[logo] ethypharm

LETTER OF PURCHASE UNDERTAKING

PRESENT

On the first part,

LABORATORIOS BELMAC, S.A. domiciled at Montearagón 9, 28033 Madrid, represented by its General Director Mr. Adolfo Herrera

Hereinafter **BELMAC**

And on the second part,

LABORATORIOS ETHYPHARM, S.A. domiciled at Marqués de Ensenada 16, 28004 Madrid, represented by its General Director Mr. Adolfo de Basilio

Hereinafter **ETHYPHARM**.

SPECIFICATIONS

1- **BELMAC** undertakes to exclusively purchase its own needs and that of its clients from ETHYPHARM, on the proviso that ETHYPHARM guarantees that said supply will occur in the time and manner established in purchase orders and at competitive market prices, and that the manufacture of the product (microgranules of OMEPRAZOLE) will be performed by BELMAC in its own installations.

2- The supply prices will be fixed by mutual agreement.

3- This letter of purchase undertaking is valid for two years and renewable for the same term provided neither of the two parties opposes this giving four months notice in writing.

And in witness of which and to due legal effect, signatures are affixed to two copies of this document at Madrid, March 23, 2000.

For Ethypharm, S.A.
[signature]

For Laboratorios Belmac, S.A.
[signature]